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GOLDBERG, J

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/398,522 | Applicant(s) ISSA, JEAN-PIERRE | |
|---|---|---|---|
| | Examiner Jeanine A Enewold Goldberg | Art Unit 1655 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-11 and 13-32* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 25-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,11 and 13-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. This action is in response to the papers filed May 15, 2001. Currently, claims 1-11, 13-32 are pending. Claims 1-9, 25-32 have been withdrawn from consideration as drawn to non-elected claims.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn.

4. This action contains new grounds of rejection.

### *Maintained Rejections*

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

5. Claims 10-13, 19, 22-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a cellular proliferative disorder in a subject by contacting a nucleic acid containing specimen with an agent that provides a determination of the methylation state of CACNA1G and detecting hypermethylation status of the gene to detect a tumor, does not reasonably provide enablement for a method for detecting a cellular proliferative disorder in a subject by contacting a nucleic acid containing specimen from the subject with an agent that provides a determination of the aberrant methylation state of APOB, CDX2, EGFR,

FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1, SDC4 whose methylation status was not previously known to be associated with a cellular proliferative disorder such that a cellular proliferative disorder may be detected. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are broadly drawn to a method for detecting cellular proliferative disorder in a subject by contacting a nucleic acid containing specimen from the subject with an agent that provides a determination of the methylation state of APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1, SDC4 and CACNA1G gene such that a cellular proliferative disorder may be detected.

The specification teaches that aberrant methylation of CGIs have been detected in genetic disease such as the fragile-X syndrome, in aging cells and in neoplasia (pg. 3, lines 21-23). The specification teaches the CpG-rich regions from APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4 which are hypermethylated (pg. 7, lines 10-11, Figures 4A-4F). The specification teaches that methylation analysis of CACNA1G was performed (pg. 24). The specification explicitly teaches that whether large CpG islands are aberrantly methylated in cancer is not apparent (pg. 24).

The art teaches that tissues are both hyper and hypo methylated as indicative of cancerous tissue. Balyin et al. (herein referred to as Balyin-1) teaches alterations in DNA methylation as a fundamental aspect of neoplasia (Advances in Cancer

Research, Vol. 72, pg. 141-196, 1998). Baylin-1 discusses not only hypermethylation as associated with cancer, but additionally teaches that hypomethylation is associated with cancer. In the discussion, Baylin-1 teaches that in a number of models of carcinogenesis decrease in numbers of methyl groups appear to begin early in tumor progression and before the appearance of frank tumor formation (pg. 151). Baylin teaches that there is a clear association of DNA hypomethylation with tumors, however, the exact ramifications of this change for steps in tumor progression are poorly understood (pg. 151). Hypomethylation patters have been described for oncogenes in tumors. Baylin also teaches hypermethylation in cancer (pg. 152). Baylin provides several examples of CpG island hypermethylation associated with transcriptional inactivation of specific genes in neoplastic cells including Rb, VHL, p16, p15, E-cadherin, hMLH1, and ER (Table 2). Further, Nelson et al. (herein referred to as Nelson) teaches a method for detecting proliferative disorder associated with glutathione-S-transferase (GSTP1) which detect hypermethylation of GSTP1 promoter in a tissue sample (abstract). As seen in Figure 5, hypermethylation does not appear to occur in normal tissues. Nelson teaches that a hypermethylated promoter for the human GSTP1 positively correlates with prostatic carcinogenesis (col. 3, lines 5-10). In a distinct article, Baylin et al. (herein referred to as Baylin-2) teaches that HIC-1 is within a CpG island which is abnormally methylated in many different types of tumors. Baylin-1 teaches hypermethylation of HIC-1 was analyzed in primary tumors and cultured cells lines (col. 22, lines 36-40).

The specification teaches APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4, are hypermethylated (pg. 7). The specification has not provided any correlation between tumor and normal tissue regarding hypermethylation for APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4 such that the skilled artisan would be able to take the information and detect cellular proliferative disorders. It would be unpredictable to what degree these specific genes are infact differentially methylated in cancerous tissue and normal tissue. And it would require undue experimentation for the skilled artisan to perform the necessary experimentation to determine whether the listed genes are only hypermethylated in specific tumors and other cellular proliferative disorders such that cellular proliferative disorder may be detected. The skilled artisan would be required to sample tumor and normal cells from a clinical study to ascertain whether the tumors are hypermethylated and then determine whether this is only observed in tumors. Genes are known to be methylated at certain stages, however, mere methylation is not necessarily indicative of cancer. Absent showing that these genes are in fact differentially methylated in tumors and normal tissue, the skilled artisan would be unable to practice the claimed invention without undue experimentation.

**Response to Arguments**

The response traverses the rejection. The claims have been amended to overcome the rejection as it previously applied to any gene.

The response asserts that the specification does provide correlation between tumor and normal tissue regarding hypermethylation of APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1, SDC4 such that the skilled artisan would be able to take the information and detect cellular proliferative disorders. The applicants point to Table 5 at page 39 of the specification to support this position. Further applicants point to Figure 4 which illustrates the CpG islands for each of these genes. This argument has been reviewed but is not convincing because the specification has not provided any information regarding the number of normal samples which were compared with the tumor samples. The specification has not provided any showings that a representative number or statistically significant number of the genes showed aberrant methylation such that cellular proliferative disorder would be indicated. It is unclear whether one sample was studied which had hypermethylation or whether a representative sample was reviewed to provide a representative analysis of the hypermethlyation of tumors. Moreover, from Table 5 it is unclear whether the tumor samples were from patients, were cell lines or of other origin. Additionally, within Table 5, the specification cites that the genes were hypermethylated in "common tumors" however, it is unclear what "common tumors" encompass. The specification does not appear to provide whether the samples were studied in all tumors, namely common tumors, leukemias, breast, prostate, and colon tumors, however were only hypermethylated in certain tissues and not in other tissues. The claims are not limited to the CpG islands which the specification has shown in Figure 4, but rather the gene as a whole or associated regulatory regions of the gene. Finally it is noted that the claims

are not limited to hypermethylated, rather the claims recite methylation, as argued in the response and illustrated in the specification.

The prior art directed to distinct genes which are hypermethylated in cellular proliferative disorders provides a clear analysis of primary tumors and cultured cell lines which were studied and which showed hypermethylation (Balyin, US Pat. 5,756,668). Similarly, Nelson provides a Southern blot to illustrate prostate cancer, normal prostate, benign hyperplasia (col. 13-14). These comparisons and information regarding the percentage and samples allows the skilled artisan to determine the degree of information which may be achieved from such analysis such that an accurate assessment of cellular proliferative disorder may be made.

Thus for the reasons above and those already of record, the rejection is maintained.

***New Grounds of Rejection***

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 10-11, 13-24 are rejected under 35 U.S.C. 102(a) as being anticipated by Toyota et al (Cancer Research, Vol 39, pg 4535-4541, September 15, 1999).

As per the e-mail from the Journal Manager at Cancer Research, the official date of publication of this information was September 11, 1999 (see attached).

It is noted that the authorship of the Toyota et al. reference is distinct from the inventorship of the instant application and that this rejection may be overcome by the filing of a 132 Katz-type declaration.

Toyota et al (herein referred to as Toyota) teaches aberrant methylation, namely hypermethylation, of CACNA1G as indicative of cellular proliferative disorder. Toyota examined regions 1-8 of CACNA1G (limitations of Claims 15-18). Toyota teaches sampling colorectal cancers, colorectal adenomas, primer gastric cancers and AML samples for methylation analysis (limitations of Claims 22, 23, 24). Toyota teaches primers which are used for analysis (pg 4536, col. 1)(limitations of Claim 19-21). Thus, since Toyota has taught every limitation of the claims, Toyota anticipates the claimed invention.

## *Conclusion*

**7. No claims allowable.**

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
July 11, 2001

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP 1800 1600

## Goldberg, Jeanine

**From:** Publicker, Stephanie
**Sent:** Monday, June 25, 2001 3:59 PM
**To:** Goldberg, Jeanine
**Subject:** FW: CANCER RESEARCH 1999 Sept. 15; 58(18):4535-41

FYI

-----Original Message-----
From: repas@aacr.org [mailto:repas@aacr.org]
Sent: Monday, June 25, 2001 3:48 PM
To: Stephanie.Publicker@uspto.gov
Subject: CANCER RESEARCH 1999 Sept. 15; 58(18):4535-41

Dear Ms. Publicker:
Thank you for your fax of June 22, 2001 concerning the official publication date of the above-referenced information. According to the United States Copyright Office, the official date of publication of this information was September 11, 1999. There is no different date for online publication.
Sincerely,

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